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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,883	04/18/2005	Michel Christian Morre	BKR-110T	9491

23557 7590 11/06/2008

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
11/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,883	MORRE ET AL.	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-80 and 85-114* is/are pending in the application.

4a) Of the above claim(s) *59,60,86-110,112 and 114* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-58,61-80,85,111 and 113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 February 2005 and 30 November 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The Declaration under 37 CFR 1.132 of Dr. Michel Morre submitted on 18 July 2008 is acknowledged. Applicant's amendment of the claims filed 18 July 2008 has been entered.

Claims 1-55 and 81-84 are cancelled. Claims 56-80 and 85-114 are pending. Claims 59, 60, 86-110, 112 and 114 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions. Claims 56-58, 61-80, 85, 111 and 113 are under examination to the extent they read on the elected species of:

A) the IL-7 conformer comprises the amino acid sequence of SEQ ID NO: 2;

B) the pharmaceutical composition further comprising a hematopoietic cell growth factor selected from SCF, G-CSF and GM-CSF;

C) the pharmaceutical composition further comprising a cytokine, which is IL-2; and

D) the pharmaceutical composition further comprising antigen derived from the hepatitis virus A, B, C or E.

Claim Rejections Withdrawn

The rejection of claims 68-85 and 113 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reciting administration of the

pharmaceutical composition to any patient, including elderly patient, and prophylaxis, is withdrawn in response to Applicant's cancellation of claims 81-84.

Claim Rejections Maintained

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(1) Claims 56-58, 61-63, 66-71, 73-77, 80, 85, 111 and 113 remain rejected under 35 U.S.C. 102(b) as being anticipated by Namen et al. (U. S. Patent No: 5,328,988, issued on 12 July 1994), as set forth in the previous office action.

(2) Claims 56-58, 61-63, 66-71, 73-75, 78-80, 85, 111 and 113 are rejected under 35 U.S.C. 102(b) as being anticipated by Ho et al. (U.S. Patent No: 5,714,141, issued on 3 February 1998), as set forth in the previous office action.

Applicant argues that the instant specification describes that "The present invention now shows, unexpectedly, that the long term activity of recombinant human IL-7 is mostly expressed by a specific 1-4; 2-5; 3-6 conformer. The present invention further shows that efficient drug substances should not only contain the above conformer as the major constituent, but should also be essentially devoid of other conformers or IL-7 molecular variants, previously considered as active products." (page 3, lines 5-10). Applicant argues that neither Namen et al., nor Ho et al., anticipates the claimed invention, because the prior art does not disclose a composition comprising the

claimed IL-7 conformer in amounts of at least 98% by weight, and is substantially free of IL-7 molecular variants or product related impurities. With regard to the disulfide bonding pattern and inherency, Applicant argues that the art generally recognizes the human !L-7 having disulfide bonds at: Cys: 1-6; 2-5; 3-4, and only computational modeling (e.g., Srinivasan et al.) hypothesized the existence of the claimed !L-7 conformer having disulfide bonds at Cys: 1-4; 2-5; and 3-6. Applicant further provides a print-out from UniProtKB/Swiss-Prot Entry P13231 (protein database) showing that the human IL-7 protein has Cys: 1-6; 2-5; 3-4 disulfide bonds. Applicant argues that the specification has compared IL-7 compositions similar to those disclosed in Namen et al. or Ho et al. with IL-7 compositions corresponding to the claimed invention and identified differences in biological activities between the compared compositions, e.g., in Examples H, I, and J. Applicant argues that the claimed IL-7 conformer differs from those taught in Namen et al. or Ho et al., and is not inherently disclosed in either of those references.

Applicant further provides Declaration under 37 C.F.R. § 1.132 by Dr. Michel Morre (“Morre Declaration”) as evidence that the claimed IL-7 compositions differ from those of the prior art and commercially available IL- 7 compositions. In the Morre Declaration, Declarant states that a very high purity of the correct IL-7 conformer is necessary to minimize or avoid immunogenicity. Declarant states that improperly folded/aggregated IL-7 conformers and other impurities arise from the standard production of IL-7 in recombinant host cells (either eukaryotic or prokaryotic host cells), and extremely low amounts of these impurities are sufficient to trigger anti-IL-7

immunogenicity. Declarant presented data showing that IL-7 expression in mammalian cells, such as CHO, before any purification is a complex mixture of various unfolded, partially unfolded, wrongly refolded or intermolecular bridged molecules. Declarant shows that incompletely refolded IL-7 molecules are also present in a commercial source. Declarant states that it would also be expected that the IL-7 produced according to Namen et al. or Ho et al. would also result in the production of a complex mixture of unfolded/folded molecules. Declarant states that unfolded or incompletely folded IL-7 molecule reveals new antigenic epitopes which induce unwanted anti-IL-7 immunogenicity. Declarant states that classical bioassays (e.g., a cell proliferation assay using a PB-1 cell line, a murine pre-B cell line) can not discriminate between glycosylated IL-7 batches containing various levels of aggregate contaminant. Declarant further shows data wherein two GMP batches with the presence of residual impurities (P01) and with >98% improved purification process (P02), exhibit difference in anti-IL-7 antibody titers in patient serum.

Applicants' argument and the Declaration of Dr. Michel Morre under 37 C.F.R. § 1.132 filed 18 July 2008 have been fully considered, but are insufficient to overcome the rejection under 35 U.S.C. 102(b) as being unpatentable over Namen et al. (U. S. Patent No: 5,328,988), or over Ho et al. (U.S. Patent No: 5,714,141) for the following reasons.

The independent claim 56 is directed to a composition of matter comprising a human or simian IL-7 conformer, wherein said conformer comprises the following three disulfide bridges: Cys: 1-4 (Cys2- Cys92); 2-5 (Cys34- Cys 129) and 3-6 (Cys47-Cys 141), wherein the total amount by weight of said IL-7 conformer in said composition of

matter is at least 98% by weight and wherein said composition of matter is substantially free of IL-7 molecular variants or product related impurities. As set forth previously, Namen et al. teaches a pharmaceutical composition comprising a substantially homogeneous recombinant human IL-7 polypeptide free of contaminating endogenous materials (col. 13, lines 38-42). Ho et al. teaches a pharmaceutical composition comprising a highly purified recombinant human IL-7 in combination with a vaccine, e.g., Hepatitis B vaccine (col. 3, lines 63-67; col. 4, line 67 bridging col. 5, line 2).

While Namen et al. is silent about the disulfide bond positions, this structural feature would reasonably have been considered to be inherent to the human IL-7 molecule since the tertiary structure of a protein is an intrinsic feature resulting from its primary structure. A compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Case law has established that the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Even though there is a dispute regarding the disulfide bond positions for human IL-7, such as Cys: 1-6; 2-5; 3-4 as recognized in the UniProtKB/Swiss-Prot database, and Cys: 1-4; 2-5; and 3-6 as recognized by Srinivasan et al., a scientific explanation for the prior art's functioning does not render the old composition patentably new to the discoverer. Further, the rh-IL-7 of Namen et al. or Ho et al. has the same biological activities and therapeutic uses as the claimed IL-7 conformer. For example, Namen et al. teaches the therapeutic compositions

comprising a purified IL-7 can be used for stimulating B and/or T lymphocyte development or proliferation, or modulating immune, lymphopoietic, or hematopoietic response in mammals, including humans (col. 16, lines 3-13). Ho et al. teaches that rh-IL-7 can improve the potency of the vaccine (modulating immune response) (col. 8, lines 12-19; col. 9, lines 43-46). Therefore, the IL-7 composition of the prior art meets each and every limitation as recited in the claims.

Applicant argues that the claimed IL-7 conformer differs in biological activities from those taught in Namen et al. or Ho et al., and such a difference is indicated in Examples H, I, and J. However, the "impure" IL-7 used in Examples H, I, and J ***is not*** comparable to the IL-7 taught in Namen et al. or Ho et al., because the prior art specifically teaches "a *substantially homogeneous rh-IL-7 polypeptide free of contaminating endogenous materials* " or "*a highly purified rh-IL-7*". The prior art protein is purified so that it can be used for therapeutic setting, e.g., administering to a human.

With respect to the Morre Declaration, while it is true that improperly folded/aggregated IL-7 conformers and other impurities can arise from the standard production of IL-7 in recombinant host cells, and such incompletely refolded IL-7 molecules are also present in a commercial source, however, Namen et al. or Ho et al. teaches rh-IL-7 used for therapeutic purposes, and as stated above, the prior art expressly teach that the IL-7 polypeptide is "*substantially homogeneous and free of contaminating endogenous materials* " or "*a highly purified*". Unpurified, partially purified, or commercially available IL-7 are usually not qualified in purity for

pharmaceutical uses. The Morre Declaration has not shown evidence that the IL-7 ***equivalent to the prior art*** is difference from the instantly claimed IL-7.

With respect to Declarant statement that extremely low amounts of impurities, i.e., unfolded, incompletely folded, or aggregated IL-7 molecule, are sufficient to trigger anti-IL-7 immunogenicity, and that such impurities can not be detected by classical bioassays (e.g., a cell proliferation assay using a PB-1 cell line, a murine pre-B cell line), however, these characteristics, e.g., immunogenicity, are not recited in the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, Applicant's arguments and the declaration are relying on properties that occur as a result of the method of making the composition as outlined in the specification. However, the claims are not set forth as product-by-process claims and it is improper to read limitations of the specification into the claims.

For these reasons, the rejection under 35 U.S.C. 102(b) as being anticipated by Namen et al. or Ho et al. is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 64 and 65 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Namen et al. (U. S. Patent No: 5,328,988), or Ho et al. (U.S. Patent No: 5,714,141), in view of Goeddel et al. (U. S. Patent No.: 5,223,408, issued on 29 June 1993), for reasons set forth in the previous office action.

Applicant argues that neither Namen et al. nor Ho et al. teaches a composition of matter comprising a human or simian IL-7 conformer as claimed in the instant application, and that Goeddel et al. does cure this defect in the teachings of Namen et al. or Ho et al., therefore, a *prima facie* case of obviousness has not been established in this matter.

Applicants' argument has been fully considered but has not been found to be persuasive.

As noted above, the instant claims remain rejected under 35 U.S.C. 102(b) as being anticipated by Namen et al. and Ho et al. Goeddel et al. cures the deficiency of the prior art by teaching conjugating an IL-7 polypeptide with IgG1-Fc or albumin to increase half-life ((col. 6, line 36; col. 19, lines 33-43). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use an IgG1-Fc or albumin conjugated-IL-7 polypeptide, which has an increased half-life, in the prior art compositions.

Claim 72 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ho et al. (U.S. Patent No: 5,714,141), in view of Morozov et al. (U.S. Patent No: 5,728,680, issued on 17 March 1998).

Applicant argues that Ho et al. does not teach a composition of matter comprising a human or simian IL-7 conformer as claimed in the instant application, and that Morozov et al. does cure this defect in the teachings of Ho et al., therefore, a *prima facie* case of obviousness has not been established in this matter.

Applicants' argument has been fully considered but has not been found to be persuasive.

As noted above, the instant claims remain rejected under 35 U.S.C. 102(b) as being anticipated by Ho et al. Morozov et al. cures the deficiency of the prior art by teaching formulating pharmaceutical compositions containing Hepatitis B vaccine with excipients, such as sodium citrate (col. 31, line 49 bridging col. 32, line 12). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include excipients, such as sodium citrate, in the prior art composition that contains rh-IL-7 and Hepatitis B vaccine.

Conclusion

NO CLAIM IS ALLOWED.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph. D.
November 3, 2008

/Elizabeth C. Kemmerer/

Primary Examiner, Art Unit 1646